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13. ABSTRACT ***(Maximum 200 Words)***

We hypothesized that the elevated risk for prostate cancer, observed in African Americans compared with whites, is present in all populations of African descent suggesting that genetic and/or shared metabolic and lifestyle factors, rather than environmental factors, are the main determinants of risk. The specific aims were to conduct a population based prostate cancer screening of the male residents, aged 50-79, on the Caribbean island of Tobago (recruitment goal, 2346 men) in order to estimate the screening detected prevalence rate of prostate cancer, and to conduct a pilot case control study (200 men) of conventional risk factors and molecular markers. This study, which we believe is the first involving screening a large Afro-Caribbean population diagnosed prostate cancer among the first 1645 screened men, aged 50-79, residing on the island of Tobago. Our data from this study support our hypothesis that, as observed in African American men, Afro-Caribbean men experience a high risk for prostate cancer. Results from the pilot case control studies suggest that sex hormone related polymorphisms and surrogate hormone measures are related to prostate cancer. This Tobago population of West African descent shares considerable genetic ancestry with African Americans and provides a uniquely valuable opportunity for the study of prostate cancer risk. The data emerging from this study is expanding our understanding of the contribution and interaction of environmental, genetic and metabolic factors to risk for prostate cancer. We expect that these findings will enable us to reduce the risk for prostate cancer among men of West African descent.

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Table of Contents

Abstract

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Idea Development Award, DAMD 17-99-1-9015 25 May, 2001

Tobago Prostate Survey: Prostate Cancer Risk in a Large Population-Based Study of Men of African Descent

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Introduction.

We hypothesized that the elevated risk for prostate cancer, observed in African Americans compared with whites, is present in all populations of African descent suggesting that genetic and/or shared metabolic and lifestyle factors, rather than environmental factors, are the main determinants of risk. The specific aims were to conduct a population based prostate cancer screening of the male residents, aged 50-79, on the Caribbean island of Tobago (recruitment goal, 2346 men) in order to estimate the screening detected prevalence rate of prostate cancer, and to conduct a pilot case control study (200 men) of conventional risk factors and molecular markers. This Tobago population of West African descent shares considerable genetic ancestry with African Americans and provides a uniquely valuable opportunity for the study of prostate cancer risk. Understanding the contribution and interaction of environmental, genetic and metabolic factors should enable us to reduce the risk for prostate cancer among men of West African descent.

Body.

Statement of Work.

Task 1. Initiation of study (Months 1-3)

Organization, ordering of supplies, training, was completed by January, 1999 (Month 3)

Task 2. Conduct PSA & DRE screening for prostate cancer in Tobago male population aged 50-79, Months 4-17.

We have recruited 1645 men aged 50-79. Ninety four percent of men reported 3 or 4 grandparents of African descent. Digital rectal exams have been completed for 1315 men, of whom findings were abnormal in 410 (31%). Serum PSA results are available for 1505 men, including 412 (27.4%) with PSA $\geq$ 4 ng/ml. Serum PSA and/or DRE were abnormal in 634 men (38.5%). Of these, 506 (80%) have undergone biopsy. Pathology results have been received for 506 biopsies, of which 218 (44%) reported a diagnosis of prostate cancer. Among the first 1645 screened men, aged 50-79, 13.5% have been diagnosed with prostate cancer. See further results under Task 6.

We had anticipated recruiting about 2346 men, aged 50-79. Two major factors have slowed recruitment. During the initial delay in funding, we had to lay off the staff and lost the momentum that we had built up during the pilot study. Subsequently, we recovered and built up good recruitment rates. However, starting around the end of

February, 2000, healthcare workers in Tobago started a work slowdown which lasted several months. This was a response to a profound budgetary crisis in the Tobago government which had severe effects on the health care system. The hospital managed to remain open, but the 19 regional clinics have been essentially shut down for more than a year. We are now in a new budget year and the system is beginning to recover, staff are being paid. But clinic phones are still out of service, and plumbing is in not working in most clinics, so that many clinics are not functioning. Our recruitment was slowed because word of mouth within the public health care system was our most effective tool. It also has been more difficult to arrange staffing for the blood draws, DREs, and biopsies.

Also, at this point, we would have to admit that our recruitment goal of 80% was extraordinarily optimistic. This was based on our previous experience in which we recruited more than 80% of a defined Tobago population into a cardiovascular risk study. The current study, however, is far more complex regarding factors influencing participation, e.g. a high level of homophobic fear of digital rectal exams (and most men have never had a digital rectal exam), deep concerns about loss of manhood related to prostate problems, and the not unusual exaggerated fear of blood draws among men. However, the deep level of community respect for our Co-PI, Alan L. Patrick, M.D., and the Tobago Prostate Survey staff, some of whom have worked with Dr. Patrick on research studies for 25 years, and our persistent public education through multiple venues including public workshops on prostate cancer, have allowed us to have remarkable success in recruiting. We are currently at about 70% of our recruitment goal. Though the DOD funding has ended, recruitment will continue under other funding and we anticipate coming close to our original recruitment goal.

Task 3. Support Regional Health Authority in scheduling and completing biopsies and provide pathological diagnosis, Months 6-21.

Trinidad has three practicing urologists and two surgeons with some urology training. Four of these five, plus two Tobago surgeons and Co-PI Dr. Patrick, have participated in ultrasound-guided, random sextant, biopsy two day training sessions conducted by University of Pittsburgh urologists on two occasions. Due to time constraints, none of the Trinidad physicians have been able to participate in regular biopsy sessions on Tobago. Instead, one biopsy session (usually 10-15 biopsies) a week is conducted by one of the two Tobago surgeons under the supervision of the Co-PI Dr. Patrick. This has worked very well. There have been no major complications. The high rate of cancer detection suggests that the surgeons are adhering well to the random sextant biopsy protocol.

Task 4. Support referral of patients for treatment for prostate cancer and follow up on treatment outcome, Months 8-30.

Patients diagnosed with prostate cancer have been counseled regarding treatment options by Co-PI, Dr. Alan Patrick or the Tobago surgeons. A treatment workshop for health professionals was conducted in January, 1999, in Tobago by a team of urologist, medical oncologist, epidemiologist from the University of Pittsburgh, and the Co-PI from Tobago. The audience of about 20 included the majority of clinicians on the island. During the past year, we have conducted three public workshops on prostate cancer treatment with participation of urologists from the University of Pittsburgh and Trinidad. Each workshop has been attended by 75-100 people.

All men with prostate cancer have been referred to the general surgical clinic at the Tobago Hospital. This is the established referral practice for prostate cancer in government hospitals. We have held numerous meetings with the Secretary, Division of Health and Social Services, Tobago, the Administrator and Health Planner, Division of Health and Social Services, Tobago, the Tobago Hospital Administrator, the County Chief Medical Officer, health officials from Trinidad, Trinidad radiologists and urologists, and Tobago clinicians, to discuss planning and resources for prostate cancer treatment, included surgery, external beam radiation, and medical treatment. The officials are currently negotiating with a Trinidad urologist to establish a semi-monthly urology clinic at the Tobago Hospital.

The Department of Urology, University of Pittsburgh, under the leadership of Dr. Joel Nelson, has embraced a commitment to volunteer surgical services to the participants in the Tobago Prostate Survey. Since November, 2000, 17 men with prostate cancer have undergone radical nerve-sparing prostatectomy at the Tobago Regional Hospital. To our knowledge, this type of surgery has never before been performed in the Caribbean. The surgeries have gone extremely well, with enormous credit due to the University of Pittsburgh surgeons, and to the local team of surgeons, OR staff, and ward staff. Local urologists and surgeons attended to observe the procedures.

Wide publicity regarding the Tobago Prostate Survey in the three major newspapers of Trinidad & Tobago has led to increased focus on the burden of prostate cancer in Trinidad as well as in Tobago. This has stimulated the development of prostate cancer treatment resources. Surgeons from the U.S. and the U.K. have visited Trinidad to help increase expertise in radical prostatectomy. Two Trinidad urologists are now collaborating with a group to Chicago to provide brachytherapy for prostate cancer in Trinidad & Tobago.

A system for followup of men diagnosed with prostate cancer has been implemented.

Task 5. Conduct pilot case control studies, Months 13-24.

Preliminary case control studies focused on conventional risk factors, HHV-8 (Kaposi's sarcoma virus) infection, bone density, and numerous candidate gene polymorphisms have been completed. See results under Tasks 6, 7.

Task 6. Analysis of screening data and conventional risk factors, Months 18-24.

New scientific findings from this study are emerging daily. The results are very exciting and several manuscripts are in preparation or planned.

The high prevalence rate reported above reflects not only the high rate of abnormal screening results, but also a high positive predictive value for an abnormal screen: 10% of biopsied men aged 40-49 were diagnosed with prostate cancer, 29% aged 50-59, 44% aged 60-69, and 58% aged 70-79. The positive predictive value of elevated PSA was similar across age groups from 50 to 79, with 57% of biopsied men diagnosed with prostate cancer. Compared with elevated PSA, the positive predictive value for DRE was much lower among men aged 50-59 (55% (PSA) vs. 22% (DRE)). However, among older men, the positive predictive values of the two screening measures were similar across age groups, approximately 50-60%, see Table 1.

Table 1. Screening and Biopsy Results for 1645 Screened Tobago Men by Age Group

Age Group	Screened N (%)	Abnormal DRE and/or PSA N (%)	Biopsied N (%)	Prostate Cancer N (%)	Ppn Screened Men Dx Prostate Ca[a] (%)
50 – 59	733 (45)	191 (26)	154 (81)	47 (31)	47/733 (6)
60 – 69	590 (36)	247 (42)	202 (82)	90 (45)	90/590 (15)
70 – 79	322 (19)	196 (61)	150 (77)	85 (57)	85/322 (26)
Total	1645	634 (39)	506 (80)	222 (44)	222/1645 (13)

[a] Proportion of screened men diagnosed with prostate cancer

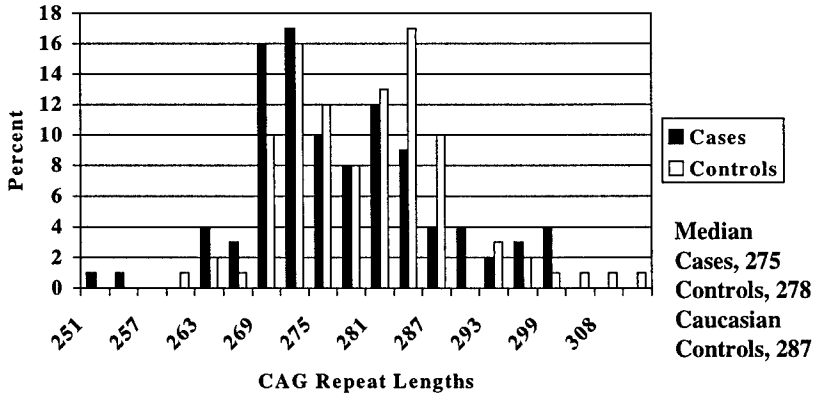
The positive predictive value of elevated PSA was similar across age groups from 50 to 79, with 57% of biopsied men diagnosed with prostate cancer. Compared with elevated PSA, the positive predictive value for DRE was much lower among men aged 50-59 (55% (PSA) vs. 22% (DRE)). However, among older men, the positive predictive values of the two screening measures were similar across age groups, approximately 50-60%. A manuscript detailing the positive predictive values of all combinations of screening parameters by age group is under preparation

Analyses of conventional risk factors were done and a paper was presented at the Caribbean Health Research Council 46th annual meeting, April 28, 2001 (Appendix). The paper is now being finalized for publication. Cases and controls were similar with respect to conventional risk factors.

Task 7. Analysis of pilot case-control data, Months 25-30.

Our proposed measurement of bone density (as a surrogate of lifetime testosterone exposure) using computer derived estimates of bone density from hand X-rays proved to be infeasible when the proposed contractor for reading the X-rays was

Distribution of Androgen Receptor CAG Repeats in Tobago Cases and Controls



23 Feb 2001

unresponsive to the task. Fortunately, this unique study attracted the collaboration of a leading bone density researcher, Dr. Jane Cauley, University of Pittsburgh. Through her non-DOD funding resources, we were able to place a new Hologistic QDR 4500 dual absorption X-ray (DEXA) machine in the Tobago Hospital, and train 3 local technicians in obtaining research quality hip and total body scans. The funding which had been reserved for reading the hand X-rays was used to fund the DEXA technicians.

The bone measurements and body fat measurements from the DEXA are very exciting. Bone density measurements in the Tobago men are generally a whole standard deviation higher than in Caucasian me (See abstract, Cauley et al). Preliminary analyses in cases and controls are still based on small numbers, but bone measurements, and central fat measurements, are consistently higher in cases than in controls in each age group (p value range 0.07 to 0.12).

We are conducting a case control study of candidate gene polymorphisms in the Tobago population. Cases are men with biopsy proven prostate cancer. In order to minimize misclassification among the controls, we have chosen men with age $\geq$ 62, normal or slightly irregular DRE exams, and PSA < 2 ng/ml. We are planning to compare 300 cases and 300 controls. Preliminary data for 150 cases and 150 controls are shown in the graph above and the following tables.

The distribution of the AR CAG length polymorphisms is dramatically different in the Tobago population than in Caucasian prostate cancer cases and controls drawn from the population of Western Pennsylvania (Modugno, Trump, Ferrell et al., manuscript, Appendix). The distribution in Tobago cases and controls is shown in the Figure. Median repeat length was 275 in Tobago cases, 278 in Tobago controls, compared with 287 in the Caucasian controls. Using the Caucasian median, 287, as a cut point to distinguish long and short alleles (see distributions in Table 2), shorter alleles were much more frequent in Tobago controls than in Caucasian controls ($p<0.0001$). Using the 287 cut point, there was no relationship between AR allele length in the Tobago cases compared with controls (Table 2). However, using the cut points determined by inspection of the distributions in cases and controls (251-269, 272-281, 284-311), the short alleles were significantly related to a two fold risk of prostate cancer (Table 2).

The absence of the estrogen receptor XbaI site was associated with a three fold risk for prostate cancer among the Tobago men, but not in the Caucasian men. However, the higher risk negative allele was significantly less frequent in the Tobago population. The estrogen receptor polymorphic site recognized by the PUVII restriction enzyme was not related to prostate cancer in univariate analyses in the Tobago population or in the Caucasian population.

The HgaI polymorphic site in the aromatase gene (Cyp 19) was not associated with prostate cancer in univariate analyses in either population.

Table 3 shows the results of categorical logistic regressions to examine the relationships between the androgen receptor genotypes and the estrogen receptor and aromatase genotypes. In both populations, heterozygous or homozygous absence of the ER XbaI restriction site increased risk for prostate cancer in the presence of either long or short AR alleles. With regard to the ER PUVII genotype, the long AR allele was equally protective across all genotypes. The short AR allele, combined with heterozygous or homozygous absence of the ER PUVII cut point, conferred higher risk in both the Tobago and Caucasian populations. The C/T aromatase genotype did not influence risk related to the AR long and short alleles in the Tobagonians, but increased risk in the presence of either long or short AR alleles among the Caucasians.

Table 2. Androgen receptor, estrogen receptor, and aromatase genotypes in the Tobago population compared with Western Pennsylvania Caucasians

		Tobago			Caucasian (Modugno, Trump, Ferrell et al)		
Gene	polymorphism	Cases	Controls		Cases	Controls	
		N (%)	N (%)	OR(95%CI)	N (%)	N (%)	OR(95%CI)
Andr Recpt	CAG repeat						
	Long (284-311)	26(27%)	36(36%)	1.0			
	Med (272-281)	46(48%)	49(50%)	1.3(0.7-2.5)			
	Short (251-269)	24(25%)	14(14%)	2.4(1.04-5.4)			
		96	99				
	Long (≥ 287)	17(18%)	19(19%)	1.0	45(56%)	116(41%)	1.0
	Short (< 287)	79(82%)	80(81%)	1.1(0.5-2.3)	36(44%)	170(59%)	1.8(1.11-3.0)
		96	99		91	286	
Estrogen							
Receptor	PUVII						
	+/+	25(17%)	29(20%)	1.0	26(32%)	99(34%)	1.0
	-/+	75(51%)	77(53%)	0.7(0.4-1.4)	34(42%)	133(46%)	0.97(0.55-1.7)
	-/-	47(32%)	39(27%)	0.8(0.5-1.4)	21(26%)	59(20%)	1.3(0.7-2.6)
		147	145		81	291	
	XBAI						
	+/+	69(47%)	87(60%)	1.0	34(41%)	139(48%)	1.0
	-/+	61(41%)	52(35%)	1.5(0.91-2.4)	38(46%)	111(38%)	1.4(0.8-2.4)
	-/-	17(12%)	7(5%)	3.1(1.2-7.8)	10(12%)	41(14%)	1.00(0.5-2.2)
		147	146		82	291	
Aromatase							
Cyp19	HgaI						
	CC	85(58%)	81(56%)	1.0	79(90%)	277(94%)	1.0
	CT	52(36%)	54(37%)	1.3(0.5-3.3)	9(10%)	19(6%)	1.7(0.7-3.8)
	TT	9(6%)	11(7%)	1.2(0.4-3.1)	88	296	
		146	146				
	All others	86(57%)	98(65%)	1.0			
	298/298	64(43%)	52(35%)	1.4(0.88-2.2)			
		150	150				

Table 3. Interactions between the androgen receptor (AR), estrogen receptor (ER) and aromatase (Cyp19) in the Tobago and Caucasian populations

		Tobago			Caucasian (Modugno, Trump, Ferrell et al)		
		Cases	Controls		Cases	Controls	Adjusted
AR	ERXba1	N (%)	N (%)	OR(95%CI)	N (%)	N (%)	OR(95%CI)
Long*	+/+	30(32%)	50(51%)	1.0	15(19%)	91(32%)	1.0
	-/+	30(30%)	31(30%)	1.6(0.8-3.2)	17(22%)	54(19%)	1.85(0.83-4.11)
	-/-	11(12%)	3(3%)	6.1(1.6-23.7)	1(1%)	21(7%)	
Short*	+/+	16(17%)	10(10%)	2.7(1.07-6.6)	14(18%)	46(16%)	2.1(0.90-4.9)
	-/+	7(7%)	3(3%)	3.3(0.92-8.1)	21(27%)	53(19%)	2.5((1.15-5.9)
	-/-	1(1%)	1(1%)		9(12%)	16(6%)	4.7(1.6-13.4)
AR	ERPuvll						
Long*	+/+	15(16%)	15(16%)	1.0	13(17%)	60(21%)	1.0
	-/+	29(31%)	44(45%)	0.6(0.3-1.6)	12(16%)	73(26%)	0.80(0.3-1.9)
	-/-	27(28%)	24(25%)	1.1(0.5-2.8)	7(9%)	33(12%)	1.14(0.4-3.3)
Short*	+/+	2(2%)	6(6%)	0.3(0.1-1.9)	11(14%)	17(13%)	1.5(0.6-3.8)
	-/+	18(19%)	7(7%)	2.8(0.93-8.1)	21(28%)	56(20%)	1.7(0.8-3.9)
	-/-	4(4%)	1(1%)		12(16%)	22(8%)	2.8(1.05-7.4)
AR	Aromatase						
Long*	C/C	43(45%)	49(51%)	1.0	33(41%)	159(56%)	1.0
	C/T	24(25%)	31(32%)	0.9(0.4-1.7)	4(4%)	10(4%)	2.5(0.6-10.4)
	T/T	5(5%)	3(3%)	1.9(0.4-8.4)			
Short*	C/C	12(13%)	6(6%)	2.3(0.8-6.6)	40(49%)	108(38%)	1.8(1.06-3.2)
	C/T	10(10%)	7(7%)	1.7(0.6-4.6)	5(6%)	8(3%)	3.9(1.14-13.5)
	T/T	2(2%)	1(1%)				

* Cut points: Tobago, long $\geq$ 272; Caucasian, long $\geq$ 287.

There were no significant differences in mean age, height, weight, waist, hips, waist-hip ratio, body mass index (kg/m^2) between Tobago cases and controls. Nor were there significant differences in any of these variables related to genotype alleles categories in Tables 2 and 3.

Our colleague, Dr. Clifford Rosen, reported last year that variable length in a dinucleotide CA repeat 1 kb upstream from the transcription start site in the IGF-I gene was associated with significant differences in serum IGF-I. In particular individuals who were homozygous for 192 base pairs had 20% lower serum IGF-I than those who were heterozygous at either allele or had other variable lengths of the dinucleotide (e.g.190,194, 196 bps),even after correction for age and sex. More recently, these data were also confirmed in a pilot study performed with Dr. Steven Plymate among 25 Caucasian men with prostate cancer. The 192/192 genotype was associated with 20% lower serum IGF-I levels than any other genotype, although the frequency of that genotype did not differ from other normal populations[1].

In our preliminary data analyses, IGF-1 repeat length polymorphisms distributions have not differed between cases and controls. Cyp11A polymorphism 216 appears to be protective against prostate cancer. Vitamin D polymorphisms were not related to prostate cancer in this population.

Table 4. Frequencies of the Cyp11a, Cyp17, IGF1, and VDR TaqI, FokI and BSM1 polymorphisms in Tobago Cases and Controls (Ferrell, Bunker, Patrick et al., unpublished data)

Gene	polymorphism	Cases	Controls	
		N (%)	N (%)	p
Cyp11A				
	216/216	7(7%)	13(19%)	
	216/226	42(46%)	21(30%)	
	226/226	43(47%)	35(51%)	
		92	69	.04
Cyp17	MSPAI			
	TT	47(32.0)	41(41.0)	
	CT	44(44.9)	44(44.0)	
	CC	12(12.2)	15(15.0)	
		98	100	.85
IGFI	184/190 – 192/202	60(60.0)	58(70.7)	
	194/194 – 200/200	40(40.0)	24(29.3)	
		100	82	.13
VDR	FokI			
	ff	4(2.7)	5(3.4)	
	Ff	42(28.8	48(32.4)	
	FF	100(68.5)	95(64.2)	
		146	148	.73
	TaqI			
	tt	10(7.1)	5(3.4)	
	Tt	55(39.0)	48(32.4)	
	TT	76(53.9)	95(64.2)	
		146	148	.73
	BSMI			
	0	10(10.1)	10(9.9)	
	1	39(39.4)	36(35.6)	
	2	50(50.5)	55(54.5)	
		99	101	.84

Key Research Accomplishments.

New findings.

- Risk for prostate cancer is much higher in this population of West African descent than in Caucasian populations. Compared with a similarly screened, predominantly Caucasian population:
  - Age-specific rates of elevated serum PSA ($\geq$ 4 ng/ml) in this population of African descent are approximately two times higher.
  - Age-specific rates of abnormal DRE are about two times higher.
  - Positive predictive value of elevated serum PSA and or/ DRE is about two times higher.
  - Age-specific rates of screening detected prostate cancer are three times higher.
- DEXA measured bone density (a surrogate indicator of lifetime testosterone exposure) in this population is one standard deviation higher than in Caucasian populations. Preliminary results suggest that bone density and central fat deposition are higher in cases and controls
- Rate of HHV-8 infection (Kaposi's sarcoma virus) is high (27 percent in controls) and associated with risk for prostate cancer, O.R. = 1.9, 95% C.I. (1.1-3.1).
- The BSMI polymorphism in the estrogen receptor is related to a 3 fold risk for prostate cancer.
- Evidence suggests an interaction between polymorphisms in the androgen and estrogen receptors increases risk for prostate cancer.
- The 216 allele in the CYP11a locus appears to be protective against prostate cancer.

New investigators attracted to prostate cancer research as a result of their involvement in the Tobago Prostate Survey:

- Clareann H. Bunker, Ph.D.
- Alan L. Patrick, M.D.
- Robert E. Ferrell, Ph.D.
- Jane Cauley, Dr.P.H.
  - These four established investigators have each significantly expanded their prostate cancer research activities, and are currently developing a grant application, planned for NCI, October, 2001, to study the molecular epidemiology of prostate cancer in a unique population of Trinidadian East Indians who, in strong contrast to the Tobagonians, experience very low risk for prostate cancer.
- Joeseph Zmuda, Ph.D., a very promising young researcher (new faculty member and former student of Jane Cauley) who has focused on molecular epidemiology of sex hormone metabolism and bone metabolism, has applied for a fellowship on molecular epidemiology of cancer.
- Iva Miljkovic, M.B.B.S., predoctoral Graduate Student Researcher, plans to study prostate cancer related molecular markers in sib pairs and in father-son pairs in the Tobago population for her dissertation.
- Michael Okobia, M.B.B.S., predoctoral Graduate Student Researcher, plans return to Nigeria to establish a cancer registry in Edo State and conduct molecular epidemiology studies in breast and prostate cancer.
- Mary Dana Phillips, M.S.W., predoctoral Graduate Student Researcher, is planning her dissertation study on patterns of alcohol use and risk for prostate cancer or benign prostatic hypertrophy in the Tobago population.
- Hillary Keenan, M.S., predoctoral Graduate Student Researcher, has coordinated a parallel pilot study of prostate cancer screening on the island of Trinidad among the population of East Indian descent, hypothesized to experience very low risk of prostate cancer in contrast to the very high risk observed among the population of West African descent on the island of Tobago.

Reportable Outcomes
Publications.

Abstracts.

1. Patrick AL, Bunker CH, Brufsky AM, Dhir R, Becich MJ. Preliminary screening results suggest high prevalence of prostate cancer in Tobago. Abstract published in program of the Annual Meeting of the Caribbean Health Research Council, April 21-24, 1999, Barbados.
2. Patrick AL, Bunker CH, Brufsky AM, Konety BR, Vivas CA, Dhir R, Becich MJ, Trump DL, Kuller LH. Positive predictive value (PPV) of prostate specific antigen ($\geq$ 4 ng/ml) and abnormal digital rectal exam for prostate cancer on the Caribbean island of Tobago. *W Ind Med J*, 2000;49(suppl 2):35(abstract).
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4. Bunker C, Patrick A, Melhem N, Dhir R, Konety B. Conventional risk factors do not predict prostate cancer in Afro-Caribbean: The Tobago Prostate Survey. *W Indian Med J* 2001 (in press), (abstract).
5. Bunker CH, Patrick AL, Konety BR, Dhir R, Becich MJ, Trump DL, Nelson JB, Kuller LH. High prevalence of PSA screening-detected prostate cancer among Afro-Caribbeans: Update on the Tobago Prostate Cancer Survey. *W Indian Med J* 2001 (in press), (abstract).
6. Jenkins FJ, Bunker CH, Patrick AL, Dhir R, Trump DL, Becich MJ. Evidence for association of human herpes virus 8 (HHV-8) with risk for prostate cancer. *J Urol* 2001 (in press), (abstract).

Presentations.

1. Patrick AL, Bunker CH, Brufsky AM, Dhir R, Becich MJ. Preliminary screening results suggest high prevalence of prostate cancer in Tobago. Abstract accepted for the Annual Meeting of the Caribbean Health Research Council, April 21-24, 1999, Barbados. Presentation made by Dr. Bunker
2. Bunker C. Epidemiology of Prostate Cancer in Populations of African Descent. Presented at A Symposium on Prostate Cancer, University of Pittsburgh Medical Center, June 19, 1999. Target audience: African American clinicians and the general public.
3. Patrick AL, Bunker CH, Brufsky AM, Richard J-R, Belle A, Konety BR, Vivas CA, Dhir R, Becich MJ, Trump DL, Kuller LH. Positive predictive value (PPV) of prostate specific antigen ($\geq$ 4 ng/ml) and abnormal digital rectal exam for prostate cancer on the Caribbean island of Tobago. Presentation by CH Bunker at 45th Annual Meeting, Caribbean Health Research Council, Port of Spain, Trinidad.
4. Zmuda JM, Cauley JA, Bunker CH, Patrick AL, Wheeler VW, Hill D, Ferrell RE. Androgen receptor polymorphism: Ethnic differences in allele frequencies and association with bone and muscle mass among Afro-Caribbean men. Abstract submitted to First International Workshop on the Genetics of Bone Disease. Davos, Switzerland, March 17-20, 2001.
5. Bunker CH, Patrick AL, Melhem NM, Dhir R, Konety BR. Conventional risk factors do not predict prostate cancer in Afro-Caribbeans: The Tobago Prostate Survey. Presentation by NM Melhem at the 46th Annual Meeting, Caribbean Health Research Council, Kingston, Jamaica, April 2001.

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1. Bunker CH, Patrick AL, Brufsky AM, Vivas CA, Dhir R, Konety BR, Becich MJ, Trump DL, Kuller LH. High prevalence of PSA screening-detected prostate cancer among Afro-Caribbeans: Preliminary results from the Tobago Prostate Cancer Survey.

Tobago Prostate Cancer Workshops.

Additional funding received/applied for based on work supported by this award.
1. R01 CA84950 Molecular Epidemiology of Prostate Cancer InTobagonians; awarded Sept 29, 1999. This grant extends the screened group to include men aged 40-49. Additional molecular markers are being studied in a large case-control study. There is no budgetary overlap with DAMD 17-99-1-9015.

Conclusions

Summary. This study, which we believe is the first involving screening a large Afro-Caribbean population, found high rates of elevated PSA ($\geq$ 4 ng/ml), ranging from 12% age 50-59, to 53%, age 70-79. Among the first 1645 screened men, residing on the island of Tobago, aged 50-79, 13% have been diagnosed with prostate. Similar data from screening of other populations of African descent have not been published. Our data from this study support our hypothesis that, as observed in African American men, Afro-Caribbean men experience a high risk for prostate cancer. Results from the pilot case control studies suggest that sex hormone related polymorphisms and surrogate hormone measures are related to prostate cancer. Prostate cancer risk was related to evidence of HHV8 infection.
This Tobago population of West African descent shares considerable genetic ancestry with African Americans and provides a uniquely valuable opportunity for the study of prostate cancer risk. The data emerging from this study is expanding our understanding of the contribution and interaction of environmental, genetic and metabolic factors to risk for prostate cancer. We expect that these finding will enable us to reduce the risk for prostate cancer among men of West African descent.

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High Prevalence of Screening-Detected Prostate Cancer Among Afro-Caribbeans: The Tobago Prostate Cancer Survey

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Abstract.

Objective: In agreement with the high risk for prostate cancer observed among African Americans, we hypothesized that the screening-detected prevalence of prostate cancer in the Afro-Caribbean Tobago population was higher than in similarly screened U.S. white populations (approximately 4%, white men aged 50-79).

Method: Male residents aged 40-79 were invited to participate in a population based screening for prostate cancer using serum prostate specific antigen (PSA) and digital rectal exam (DRE). Men with elevated PSA ($\geq$ 4 ng/ml) or abnormal DRE were offered an ultrasound guided sextant prostate biopsy.

Results: 2129 men aged 40-79 underwent prostate cancer screening between September, 1997 and January, 2001. Mean age was 56.3 years, S.D. 10.5, median 55.0. Mean serum PSA was 16.2 ng/ml, S.D. 410 (excluding 3 values $\geq$ 2 s.d. above the mean [1112, 1818, and 18330 ng/ml] mean PSA was 5.8 ng/ml, s.d. 31), median PSA 1.5 ng/ml. Elevated PSA and/or abnormal DRE was observed in 32% (675/2129) overall, and in age groups 40-49 (73/865, 11%), 50-59 (178/630, 28%), 60-69 (237/522, 45%), and 70-79 (187/292, 64%). Ten percent (203/504) of 504 men biopsied, or 10% of the 2129 screened, were diagnosed with prostate cancer. Among men aged 50-79, prostate cancer prevalence was 14% (198/1444).

Conclusion: Prevalence of prostate cancer in this population of West African descent was about three fold higher than in U.S. whites. These data support the hypothesis that populations of African descent share genetic and/or lifestyle factors which contribute to their elevated risk for prostate cancer.

Introduction.

Prostate cancer is a very serious personal and public health problem affecting African Americans more frequently than Caucasians. Based on 1990-97 data from the U.S. Cancer Surveillance Program (SEER) of the National Cancer Institute[1], age-adjusted incidence of prostate cancer is 225/100,000 among African Americans compared with 149/100,000 among white non-Hispanics. The mortality rate from prostate cancer was more than two-fold higher among persons of African descent (54/100,000) compared with white non-Hispanics (23/100,000). Incidence of prostate cancer in the U.S. increased dramatically in both groups between the late 1980's and 1993 reflecting the earlier diagnosis which occurred with the increasing use of serum prostate specific antigen (PSA) screening[1]. An encouraging downturn in prostate cancer mortality rates was observed in both ethnic groups, 1993-1997[1].

Established risk factors for prostate cancer include age, ethnicity, family history of prostate cancer, and high fat or meat diet[2]. Other factors suspected include hormone metabolism,[3 4] Vitamin D metabolism,[5] and a few occupational exposures[6]. The relationships of a number of candidate genes to prostate cancer are under investigation with most published results limited to Caucasian populations[7]. The reasons for the higher risk for prostate cancer among African Americans are unknown.

Until recently, there has been little solid prevalence, incidence or mortality data for populations of African descent outside the U.S., though data published a few years ago in an annual summary of worldwide data suggested high rates of prostate cancer mortality in Martinique and Trinidad & Tobago[8]. Glover et al. reported high rates of prostate cancer incidence in the predominantly Afro-Caribbean population of Jamaica[9]. Data regarding

screening parameters and prevalence of prostate cancer in populations of African descent in the U.S are sparse,[10 11] and virtually absent in other populations of African descent. However, a recent publication has estimated prostate cancer prevalence for 1994 among African Americans and whites using a model based on incidence and survival functions calculated from the Connecticut Tumor Registry, 1940-1993, and applied to the SEER 1973-1993 populations. The prevalence proportion ranged from 7/100,000, aged 40-44, to 9725/100,000, aged 75-79 in whites, compared with 14/100,000, aged 40-44, to 10945/100,000 in African Americans, aged 75-79[12].

We hypothesize that risk for prostate cancer is high among populations of African descent living in diverse environments. If so, this would support a hypothesis that populations of African descent share genetic and/or lifestyle factors which increase risk for prostate cancer.

On the Island of Tobago, Trinidad & Tobago, we are conducting a population-based, longitudinal study of prostate cancer in the male population aged 40-79 yrs. Here we are reporting data from the initial cross-sectional screening using serum prostate specific antigen (PSA) and digital rectal exam (DRE). This study will allow estimation of screening parameters, and prevalence. Longitudinal followup screening is planned to estimate incidence. A nested study of cases and controls will be conducted to investigate the influence of family history, body weight and body weight distribution, meat intake markers, sex hormone markers, occupational exposures, and a number of candidate genetic markers for prostate cancer risk.

Materials and Methods.

Population: The island of Tobago is about 7 by 29 miles in size. According to the 1990 census[13] of Trinidad & Tobago, the male population of Tobago, aged 40-79, numbered 5121. Ninety-two percent of Tobago residents reported that they were of African descent. Most health care is provided by a government-supported system through the Tobago Regional Health Authority which manages the 19 neighborhood health centers and one hospital. Some residents travel to Trinidad for specialized care under the government system. Some care is provided by private care-givers. PSA testing has been available but generally limited to symptomatic men seeking care in the private sector.

Recruitment: The 1990 census of Trinidad & Tobago enumerated 5121 male residents aged 40-79. Informing by health care workers the casualty department and in general clinics at the hospital and health centers, informing by private physicians in general practice, posters, flyers, public service announcements, public presentations by oncologists and urologists from Trinidad and the U.S., and word of mouth have been the primary recruitment methods.

Informed consent. Consent was obtained using forms and procedures approved by the University of Pittsburgh Institutional Review Board and the Tobago Ministry of Health.

Data collection: Data were collected by locally resident study staff at the study office located at the Tobago Regional Hospital. Data collected include ethnicity, education, occupation, smoking, medical history, personal and family cancer history, vasectomy, prostate symptoms, health screening history, alcohol intake, detailed occupational history, and height, weight, waist and hip measurements.

Biological sample collection: A 15 ml plain vacutainer of peripheral blood was drawn from fasting subjects. Aliquots of serum were frozen at -20$^{\epsilon}$C for later measurement of PSA.

Digital rectal examination (DRE): A systematic DRE was performed by a physician trained according to the study protocol. This exam was scheduled after the blood draw in order to avoid an artifactual increase in serum PSA which may follow digital manipulation of the gland.

PSA measurement: Serum PSA levels were measured at the University of Pittsburgh Central Pathology Laboratory using the automated Microparticle Enzyme Immunoassay, Abbot AxSYM PSA assay (Abbott Laboratories, Abbott Park, IL, USA).

Criteria for referral for prostate biopsy: Subjects were referred to the Tobago Regional Hospital for biopsy if the DRE was abnormal (except for simple enlargement without palpably abnormal areas) or if serum PSA was elevated ($\geq$ 4.0 ng/ml).

Prostate biopsy: Prostate biopsies were performed by urologists, or by surgeons trained by urologists from the University of Pittsburgh Medical Center. Trans-rectal ultrasound guided biopsy was performed using an 18 gauge, 21 cm spring-loaded biopsy needle (Boston Scientific, Natick MA). Sextant biopsies were obtained according to a standard protocol.

Prostate pathology: The formalin preserved specimens were stored at room temperature and shipped to the University of Pittsburgh for histopathologic examination. The specimens were examined for presence or absence of high grade prostatic intra-epithelial neoplasia (PIN), presence or absence of cancer, Gleason score of cancer, location of cancer, and peri-neural invasion.

Data analysis: Age-specific rates/100,000 were calculated. In order to be consistent with U.S. SEER publications, age adjusted rates/100,000 and standard error/100,000 were calculated by

direct standardization[14] based on the age distribution (50-79) of the 1970 U.S. standard million population[1]. Positive predictive value of the screening tests was calculated as number of men diagnosed with prostate cancer divided by the number of men with abnormal DRE and/or elevated PSA who underwent biopsy. All statistical calculations were performed using SPSS 10.0 for Windows (SPSS, Chicago, IL).

Results.

PSA and/or DRE screening was completed for 2129 men, aged 40-79. Mean age was 56.3 years, S.D. 10.5 years, median 55.0 years, range 40-79. Ninety three percent of men reported 3 or 4 grandparents of African descent, while 2.4% reported one or two of African descent. Twenty three percent had completed secondary school or higher education. Forty two percent reported ever smoking, while 14% were current smokers.

The serum PSA range was 0.1-18,330 ng/ml. Mean serum PSA was16.2 ng/ml, S.D. 410. After excluding 3 values $\geq$ 2 S.D. above the mean [1112, 1818, and 18330 ng/ml] mean PSA was 5.8 ng/ml, s.d. 31), median PSA 1.3 ng/ml. range 0.1-602 ng/ml.

Screening results are shown in Table 1. Elevated serum PSA levels ($\geq$ 4 ng/ml) were observed in 398/2040 men (20%), ranging from 2% of men aged 40-49, to 53% of men aged 70-79. DRE was abnormal in 455/1808 (25%). Frequency of abnormal DRE increased across age groups from 11% to 48%. PSA and/or DRE were abnormal in 675/2129 (32%). Thus, a high proportion of the screened men was referred for biopsy: 11% of men aged 40-49, 28%, aged 50-59, 45% aged 60-69, and 64% aged 70-79.

Of the 675 men referred for prostate biopsy, 504 (75%) have undergone biopsy. Among these 504 men, 203 (40%) were diagnosed with prostate cancer, 2 (1%) with Gleason grade 5, 121 (60%) grade 6, 62 (30%) grade 7, and 18 (9%) grades 8, 9,10. The prevalence of prostate cancer among screened men was 10% among men aged 40-79, and 14% among men aged 50-79. The age specific results are shown in Table 1.

The direct age adjusted screening detected prostate cancer prevalence rate in Tobago men, aged 50-79, was13,500/100,000, S.E. 870/100,000. This was significantly higher ($p<0.0001$)

than the similarly adjusted rate of 3,976/100,000, S.E. 238/100,000, in a population of 6501 U.S. men (92% Caucasian, 3% African American, 5% other), aged 50-79, reported by Richie et al.[16] The unadjusted prevalence in Tobago was approximately three-fold higher than in the U.S. population in each age group (Table 3, Column 7).

The high prevalence rate reported above reflects not only the high rate of abnormal screening results, but also a high positive predictive value for an abnormal screen: 10% of biopsied men aged 40-49 were diagnosed with prostate cancer, 29% aged 50-59, 44% aged 60-69, and 58% aged 70-79. The positive predictive value of elevated PSA was similar across age groups from 50 to 79, with 57% of biopsied men diagnosed with prostate cancer. Compared with elevated PSA, the positive predictive value for DRE was much lower among men aged 50-59 (55% (PSA) vs. 22% (DRE)). However, among older men, the positive predictive values of the two screening measures were similar across age groups, approximately 50-60%, see Table 1.

Among 106 men reporting family history of prostate cancer, 99 reported one relative, 5 reported two, and two reported three relatives with prostate cancer. The distribution of relatives included 73 fathers, 31 brothers, 2 half-brothers, 5 uncles, and 3 grandfathers. Ten (9.4%) of 106 men reporting family history of prostate cancer were diagnosed with prostate cancer, compared with 193 men (9.5%) diagnosed with prostate cancer among 2023 men not reporting family history of prostate cancer.

Using the 1990 census to approximate the denominator, the recruited population represents approximately 42% (2129/5121) of the Tobago male population aged 40-79. Due to the recruitment methods, there was opportunity for self referral bias, e.g. screening-detected prevalence rates could have been biased toward higher than true rates due to higher self referral

rates among men already symptomatic with prostate cancer. To examine the possible size of such a bias, the data were reanalyzed among 1765 men remaining after excluding 364 men who reported that a doctor had previously told them they had a problem with their prostate; and among 911 men who reporting waking to urinate not at all or only once per night (Table 2). Exclusion of the 'sypmtomatic' men did not lower the age-specific prevalence rates of prostate cancer in this population (Table 2). In fact, among the 70-79 year old men, there was a trend toward higher prevalence of prostate cancer after excluding the 'sypmtomatic' men.

Discussion.

The screening detected prevalence of prostate cancer in this Afro-Caribbean population, age 50-79, was about three times higher than rates reported from screening studies of predominantly Caucasian populations which reported results by age group [15 16 17]. These U.S. studies were conducted between 1989-1992 when PSA screening was just beginning to be widely used in the United States. Comparison of the rates of abnormal screening findings, and of positive predictive value of the abnormal screen, between Tobago and a large U.S. study, by Richie et al.,[16] of 6501 U.S. men (92% Caucasian, 3% African American, 5% other), aged 50-79, are shown in the Figure. The higher prevalence of prostate cancer in Tobago was due to both a higher proportion of men with abnormal screening findings in all age groups, as well as a higher positive predictive value of an abnormal screen in all age groups, compared with the U.S. population[16]. The biopsy rate among men with abnormal screening results was similar in the two studies, 75% in the Tobago study compared with 69% in the study by Richie et al.[16]. Additional factors which may influence the comparison of the screening results from these two populations include the biopsy protocol, prior level of screening in the populations, and recruitment methods. In the study by Richie et al. [16], quadrant ultrasound guided needle biopsies were performed while the current study required sextant biopsies. The use of sextant biopsies may have decreased the false negative rate in the current study, thus increasing the ascertainment of cases. However, this difference would be unlikely to make a large contribution to the observed three-fold difference in rates.

The U.S. population in the previously mentioned study[16] was screened in 1991-1992, a period during which the incidence of prostate cancer was rising sharply[1], reflecting increasing use

of PSA testing. Thus, some prostate cancer cases may have been removed from this U.S. population by prior screening. However, 18% of the Tobago men age 50-79 reported a prior PSA or blood test for prostate cancer suggesting that some level of screening had also been available in this population.

Both the U.S. [16] and the Tobago populations were self-referred. The Tobago population was recruited primarily public notice and word of mouth. The U.S. population was recruited by advertisement. Among the U.S. population, 53% reported symptoms of prostatism. Sixty-one percent (877/1444) of Tobago men, aged 50-79, prior BPH diagnosis, or waking to urinate 2 or more times per night. However, exclusion of men reporting these factors had little impact on the prevalence rate of prostate cancer. These comparisons suggest that self-referral bias was not a major contributor to the high prevalence rate of prostate cancer observed in Tobago.

Similar prevalence data from screening of other populations of African descent have not been published. A recent Our data suggest that prevalence of prostate cancer in Tobago is at least as high as among African Americans, and possibly higher.

One of the known risk factors for prostate cancer is ethnicity, i.e. African descent, though we do not know how this risk is mediated. One hypothesis is that genetic factors contribute to the high risk for prostate cancer among populations of African origin. If the white admixture rate in the Tobago population is indeed low, then this population may carry a higher burden of high risk genes of African descent than the more admixed populations in the U.S.

Conclusions.

The higher risk for prostate cancer among African Americans compared with Caucasians is well established based on incidence and mortality data[1]. Incidence data for prostate cancer in Tobago are not available, and mortality data would be based on small numbers. However, based on the screening-ascertained prevalence of prostate cancer which is approximately three-fold higher than observed among Caucasian participants in US based screening studies conducted in a generally similar manner, we are able to conclude that the risk for prostate cancer is high in the Tobago population. High risk for prostate cancer was also recently reported in Jamaica based on high incidence rates[9]. Since these U.S. and Caribbean populations presumably experience different environmental exposures, these data support the hypothesis that populations of African descent share genetic and/or lifestyle factors which contribute to their elevated risk for prostate cancer. Understanding the contribution and interaction of environmental, genetic and metabolic factors may lead to measures to reduce the risk for prostate cancer among men of West African descent in the Caribbean, the U.S., and other geographic areas.

Table 1. Prostate cancer screening among 2129 men, aged 40-79, Tobago, 1997-2000.

Age Group	Screening Criteria	n/N(%) Abn Screen	n/N(%) Biopsied	n/N(%) Prostate Ca	n/N(%) Prevalence
40-49	PSA≥ 4ng/ml	12/647(2)	5/12(42)	1/5(20)	1/647(0.2)
	Abn DRE	63/553(11)	47/63(75)	4/47(9)	4/553(1)
	PSA and/or DRE Abn	73/685(11)	51/73(70)	5/51(10)	5/685(1)
50-59	PSA≥ 4ng/ml	73/605(12)	53/73(73)	29/53(55)	29/605(5)
	Abn DRE	130/528(25)	99/130(76)	22/99(22)	22/528(4)
	PSA and/or DRE Abn	178/630(28)	136/178(76)	39/136(29)	39/630(6)
60-69	PSA≥ 4ng/ml	161/503(32)	127/161(79)	69/127(54)	69/503(14)
	Abn DRE	139/469(30)	112/139(81)	51/112(46)	51/469(11)
	PSA and/or DRE Abn	237/522(45)	183/237(77)	81/183(44)	81/522(16)
70-79	PSA≥ 4ng/ml	152/285(53)	112/152(74)	69/112(62)	69/285(24)
	Abn DRE	123/258(48)	91/123(74)	56/91(62)	56/258(22)
	PSA and/or DRE Abn	187/292(64)	134/187(72)	78/134(58)	78/292(27)
Total	PSA≥ 4ng/ml	386/1393(28)	292/386(76)	167/292(57)	167/1393(12)
50-79	Abn DRE	392/1255(31)	302/392(77)	129/302(43)	129/1255(10)
	PSA and/or DRE Abn	602/1444(42)	453/602(75)	198/453(44)	198/1444(14)
Total	PSA≥ 4ng/ml	398/2040(20)	297/398(75)	168/297(57)	168/2040(8)
40-79	Abn DRE	455/1808(25)	349/455(77)	133/349(38)	133/1808(7)
	PSA and/or DRE Abn	675/2129(32)	504/675(75)	203/504(40)	203/2129(10)

Table 2. Prostate cancer rates in the total screened population compared with rates after exclusion of men with probable prostate related symptoms.

Age Group	Total Screened		No report doctor told had prostate problem[1]		No report nightly waking twice or more to urinate[2]	
	N	% Prost Ca	N	% Prost Ca	N	% Prost Ca
40-49	685	0.7	601	0.7	420	0.7
50-59	630	5.7	538	6.7	291	6.5
60-69	522	14.6	413	15.3	163	13.5
70-79	292	23.5	213	26.8	37	32.4

[1] Excluded men who reported that a doctor had told him he had a problem with his prostate.
[2] Excluded men who reported waking twice or more often each night to urinate.

Table 3. Estimated 1994 Prevalence of Prostate Cancer based on SEER Incidence and Mortality Rates, 1973-1993, and Screening Detected Prevalence of Prostate Cancer in 1991-1992 in a Predominantly White U.S. Population and in 1997-2000 in a Predominantly African Descent Tobago Population.

Age Group	(1) SEER (1994) White Prev /100,000	(2) Screened (1991-92) White Prev /100,000	(3) Ratio Whites Screened/ SEER Whites	(4) SEER (1994) Afric Amer Prev /100,000	(5) Screened (1997-2000) Tobago Prev /100,000	(6) Ratio Tobago Screened/ SEER Afric Amer	(7) Ratio Tobago Screened/ Whites Screened
40-44	7			14	0		
45-49	39			58	1401	24.2	
50-54	220	2016	4.7	384	4899	12.8	3.1
55-59	724			1260	7774	6.2	
60-64	2041	4157	0.8	2906	12857	4.4	3.7
65-69	4319			5689	18595	3.3	
70-74	7245	7253	1.1	9474	24725	2.6	3.7
75-79	9725			10945	30000	2.7	

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(O – 65)

Conventional risk factors do not predict prostate cancer in the Afro-Caribbean: the Tobago prostate survey

CN Bunker, AL Patrick, N Melhem R Dhir, B Konety
The University of Pittsburgh, Pittsburgh PA and the Division of Health and Social Services, Tobago

Objective: To compare hypothesized risk factors in prostate cancer cases and normal controls in the island of Tobago.

Design and Methods: 1875 men aged 40 to 79 years were screened using the serum prostate specific antigen (PSA) and the digital rectal exam (DRE). Subjects with elevated PSA (> 4 ng/ml) or abnormal DRE screening were referred for a biopsy. Age-stratified analysis was conducted using four categories of 10 years each.

Results: 9.7% of the screened population was diagnosed with prostate cancer (181/388 biopsies). These were compared to 1256 normal controls with PSA < 4 ng/ml and normal DRE. Cases and controls in each of the age categories were similar with respect to education, marital status, and work status. No statistically significant differences were found between cases and controls in each of the age categories with respect to hypothesized risk factors: height, body mass index, waist circumference, agricultural chemical exposure, prostate symptoms, family history of prostate and other cancers, vasectomy and aspirin intake. However, cases 50-59 years old were slightly more likely to have a family history of cancer than controls (36.4% vs 23.3% respectively, $p = 0.095$) and less likely to have gonorrhoea ($p = 0.023$). Cases and controls were not different in reporting prostate symptomatology.

Conclusions: Prostate cancer in this population of West African descent was not associated with any of the hypothesized environmental risk factors.

Caribbean Health Research Council
46th Annual meeting, April 26-28, 2001
Kingston, Jamaica

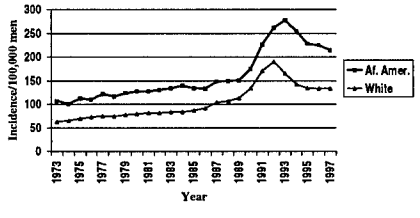
Conventional Risk Factors Do Not Predict Prostate Cancer in Afro-Caribbeans: The Tobago Prostate Survey

Clareann H. Bunker, Ph.D., Alan L. Patrick, MD., Nadine M. Melhem, MPH., Rajiv Dhir, Ph.D., Badrinath R. Konety, MD.

Background: Racial Differences

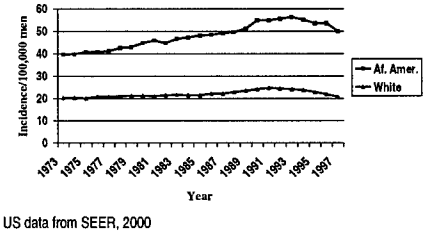
- **Incidence and mortality rates are:**
  - Lowest: Asians followed by South Americans, Southern Europeans, and Northern Europeans *(Angwafo, 1998)*
  - Highest: African descent
- **Incidence (1990-1997): 225.0/100,000 for African-Americans vs. 145.8/100,000 for Caucasians in the US** *(SEER, 2000)*
- **Mortality (1990-1997): 54.1/100,000 vs. 23.3/100,000, respectively in the US** *(SEER, 2000)*
- **Incidence: 314/100,000 in Afro-Caribbeans from Jamaica** *(Glover et al., 1998)*

Age-Adjusted Incidence of Prostate Cancer in the US[1]



[1] US data from SEER, 2000

Age-Adjusted Mortality Rates for Prostate Cancer in the US[1]



[1] US data from SEER, 2000

Environmental Risk Factors: Anthropometric Measures

- **RR=1.23-1.59 with increasing height** *(Hebert et al., 1997)*
- **RR=1.7 (BMI>27.8/BMI<23.6)** *(Cerhan et al., 1997)*
- **Excess risk of death with BMI (RR= 1.40); height (RR=1.28); and LBM (RR=1.26)** *(Andersson et al., 1997)*
- **No evidence of an association** *(Giovannucci et al., 1997; Nilsen et al., 1999; Hsieh et al., 1999; Habel et al., 2000; Schuurman et al., 2000; Shannon et al., 2000)*

Environmental Risk Factors: Occupational Exposure

- **Increased risk (RR=2.2) among farmers 70 years or older** *(Parker et al., 1999)*
- **Elevated mortality among farmers (PMR=112) and in the agriculture industry (PMR=110)** *(Buxton et al., 1999)*
- **Increased incidence ratio (SIR=1.13) among pesticide applicators in Sweden** *(Dich & Wiklund, 1998)*
- **Increased risk for soap & perfume manufacturing and leather processing** *(Sharma-Wagner et al., 2000)*
- **Tire and rubber manufacturing was not associated with prostate cancer** *(Stewart et al., 1999)*

Environmental Risk Factors: Chronic Diseases

- **Coronary Heart Disease:**
  - OR=2.00 (1.18-3.39) *(Neugut et al., 1998)*
- **Diabetes:**
  - RR=.75 (.59-.95) *(Giovannucci et al., 1998)*
  - No evidence of an association *(Hsieh et al., 1999)*

Behavioral Risk Factors

- **Cigarette Smoking**
  - Current smoking 20+ cig/day vs. never smoking: RR=2.9 *(Cerhan et al., 1997)*
  - No evidence of an association *(Neugut et al., 1998; Hseih et al., 1999; Lotufo et al., 2000)*
- **Non-Steroidal Anti-Inflamatory Drugs (NSAIDs):**
  - RR=.34 (.23-.58) *(Nelson & Harris, 2000)*
  - No evidence of an association *(Neugut et al., 1998; Norrish et al., 1998)*
- **Physical activity, diet (fat intake, carotenoids intake, vitamins), vasectomy**

Design & Methods

- ***Population:*** **Males of the Caribbean Island, Tobago, aged 40 to 79 years**
- ***Recruitment:*** **Health care workers, posters, flyers, public service announcement, word of mouth**
- ***Screening:*** **Prostate Specific Antigen (PSA) and Digital Rectal Exam (DRE)**
- ***Biopsy referral:*** **PSA ≥ 4 or abnormal DRE**
- ***Criteria***
  - Cases: Gleason score > 0 (n=204)
  - Controls: PSA < 4 and normal DRE (n=1108)

Results

- **Increased prevalence with age**
  40-49, 1.1%; ***50-59***, 10.4%; ***60-69***, 26.1%; ***70-79***, 47.8% (P=.000)
- **Age-stratified analysis: 40-59 & 60-79**
- **No difference in education, marital status, and working status**
- **No statistically significant difference in height, weight, waist, hips, and BMI**

Results (cont'd)

Occupational Exposure	Age (years)			
	40-59		60-79	
	OR	95% CI	OR	95% CI
Farming	**1.3**	**.7-2.4**	**1.1**	**.7-1.6**
Fertilizers use	**.6**	**.2-1.7**	**.7**	**.4-1.3**
Pesticides use	**.8**	**.3-2.0**	**.8**	**.4-1.4**
Fishing	**.9**	**.4-2.1**	**.8**	**.4-1.3**

Results (cont'd)

Chronic Diseases	Age (years)			
	40-59		60-79	
	OR	95% CI	OR	95% CI
Arthritis	***2.7***	***1.2- 6.1***	**.9**	**.6- 1.5**
Hypertension	**.9**	**.5- 1.9**	**1.1**	**.7- 1.6**
CHD	**1.4**	**.2- 11.1**	**.8**	**.3- 1.8**
Diabetes	**1.0**	**.3- 2.9**	**.8**	**.5- 1.2**

Results (cont'd)

Behavioral Risk Factors	Age (years)			
	40-59		60-79	
	OR	95% CI	OR	95% CI
Smoking				
11-20	*4.2*	*1.0- 17.4*	.4	.2- .8
21+	*7.6*	*1.6- 36.2*	.5	.2- 1.3
NSAIDs	1.6	.7- 3.5	1.1	.7- 1.8

Results (cont'd)

Symptomatology	Age (years)			
	40-59		60-79	
	OR	95% CI	OR	95% CI
Wake up to urinate	1.3	.7- 2.4	*1.6*	*1.0-2.5*
Prostate problems	2.2	.6- 7.5	1.6	.9-2.8
BPH	1.8	.5- 6.3	1.4	.8-2.3
Inflamed prostatitis	2.2	.3- 18.4	.7	.2-2.3
Colorectal polyps	*3.0*	*1.2- 7.6*	1.2	.5-2.9

Results (cont'd)

Family History, & Prior Screening	Age (years)			
	40-59		60-79	
	OR	95% CI	OR	95% CI
FX any cancer	1.8	.9- 3.5	.9	.5-1.4
FX prostate ca	1.2	.3- 3.9	1.6	.6-4.2
Prior DRE	*2.3*	*1.2- 4.4*	1.1	.7-1.7
Prior PSA testing	*2.9*	*1.4- 6.1*	.7	.5-1.2

Conclusion

- **Prostate cancer does not seem to be predicted by the conventional or expected environmental risk factors in this population of West African descent**
- **Studies of genetic susceptibility to prostate cancer in this population are underway**

(O – 46)

High prevalence of prostate specific antigen screening-detected prostate cancer among Afro-Caribbeans: update on the Tobago Prostate Cancer Survey

CH Bunker, AL Patrick, BR Konety, R Dhir, MJ Becich, DL Trump, JP Nelson, LH Kuller
University of Pittsburgh, Pittsburgh, USA, Tobago House of Assembly, Division of Health and Social Services, Tobago

Objectives: To determine the screening-detected prevalence of prostate cancer in the predominantly Afro-Caribbean population on the island of Tobago.

Methods: Male residents aged 40-79 years were invited to participate in a population-based screening for prostate cancer using serum prostate specific antigen (PSA) and digital rectal exam (DRE). Men with elevated PSA (> 4 ng/ml) and/or abnormal DRE were offered an ultrasound guided sextant biopsy of the prostate gland.

Results: Screening data were analyzed for the first 1784 of the 4000 men in the target population. Elevated PSA and/or abnormal DRE was observed in 31% (556/1784) overall, and in age groups (years) 40-49 (52/542, 10%), 50-59 (138/528, 26%), 60-69 (202/457, 44%), and 70-79 (164/257, 64%). Of 385 men biopsied, 163 (45%) were diagnosed with prostate cancer (9% of screened men aged 40-79 years; 13% of screened men aged 50-79 years). Gleason grade 5-7, was observed in 90% (147/163), grades 8-10 in 10% (16/163).

Conclusions: These preliminary screening results suggest a high risk for prostate cancer in this population of African descent, as is observed, based on incidence data, among African Americans. Since these populations presumably experience different environmental exposures, these data support the hypothesis that populations of African descent share genetic and/or lifestyle factors which contribute to their elevated risk for prostate cancer.

High Prevalence of PSA Screening Detected Prostate Cancer Among Afro-Caribbeans: Update on the Tobago Prostate Cancer Survey

CH Bunker, AL Patrick, BR Konety, R Dhir, MJ Becich, DL Trump, JB Nelson, LH Kuller

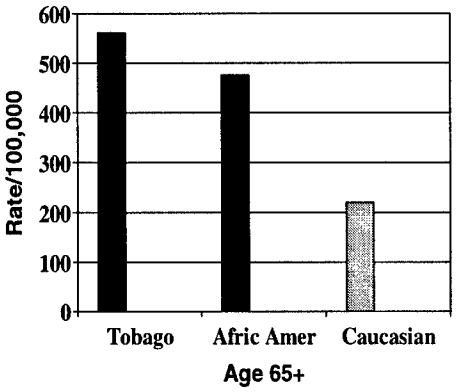
CHRC Jamaica 27 April 2001

Tobago Prostate Survey

- Dr. A. Patrick
- Dr. V. Wheeler
- Dr. J.-R. Richard
- Dr. A. Belle
- Mr. A. Bernard
- Mr. D. Guy
- Mrs. L. Phillips and Survey Staff

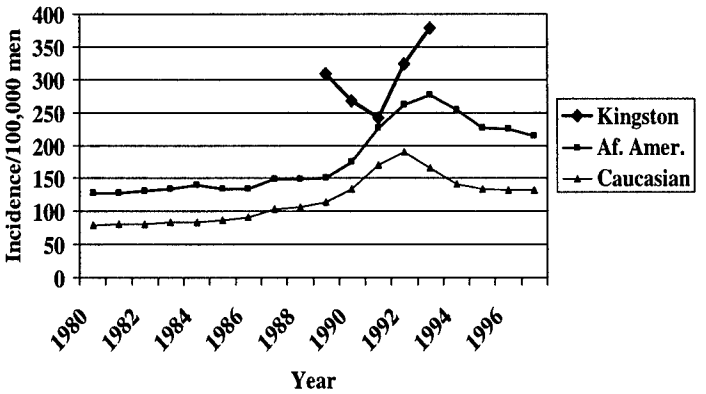
CHRC Jamaica 27 April 2001

Annual Prostate Cancer Mortality/100,000, Tobago, 1990-1994



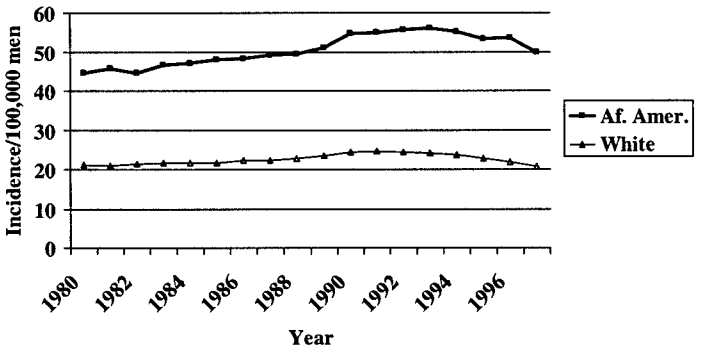
U S data from SEER, 1988-92, age-adjusted to U S 1970 pop

Incidence of Prostate Cancer in US and Jamaica[1]



[1] Glover et al., 1998; US data from SEER, 2000

Age-Adjusted Mortality Rates for Prostate Cancer in the US[1]

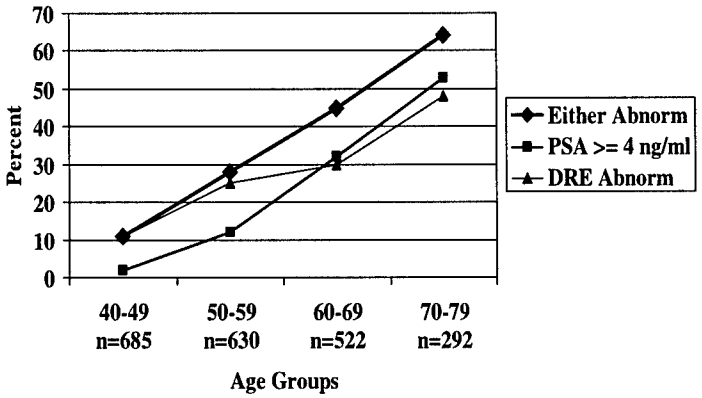


[1] US data from SEER, 2001

Tobago Prostate Survey Screening

- Population-based recruitment, 4000 men aged 40-79
- Serum prostate specific antigen
  - abnormal if $\geq$ 4 ng/ml
- Digital rectal exam
  - all abnormalities except simple enlargement
- Sextant ultrasound-guided biopsy

PSA and DRE Screening, Tobago, February, 2001



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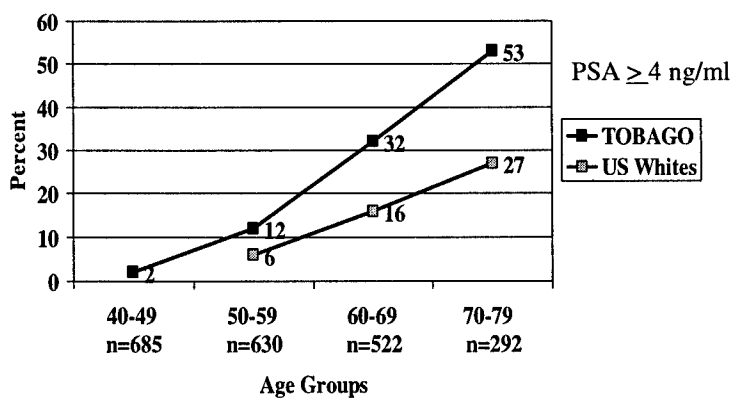
PSA Screening, Tobago, February, 2001, US Whites, 1992 (Ritchie et al)



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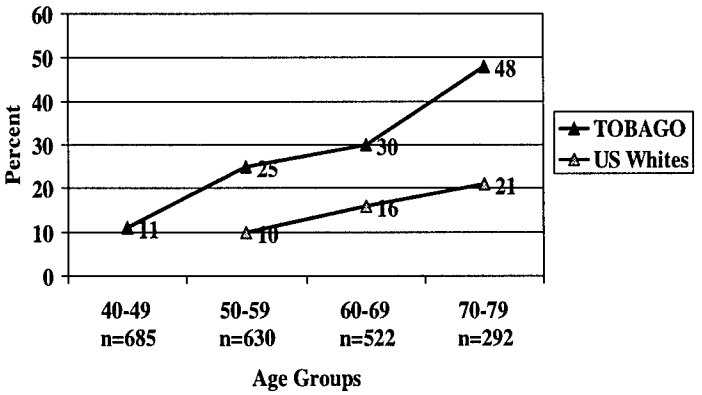
DRE Screening, Tobago, February, 2001, US Whites, 1992 (Ritchie et al)



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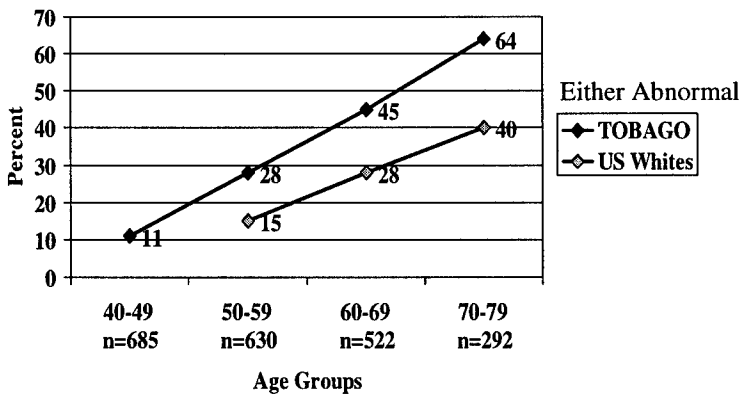
PSA and/or DRE Abnormal, Tobago, February, 2001, US Whites, 1992 (Ritchie et al)



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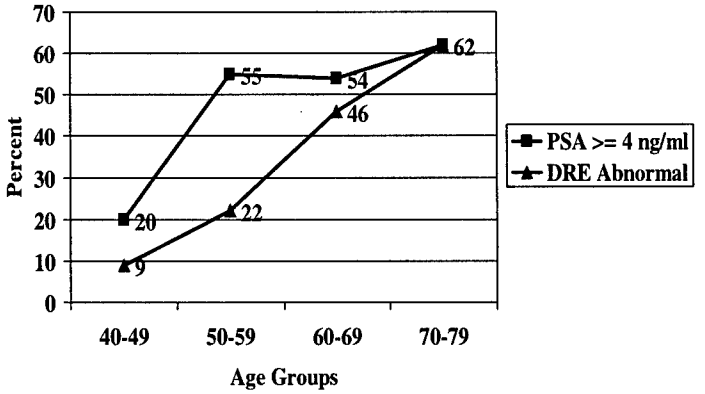
Cancer Detection Rates, PSA and DRE Screening, Tobago, February, 2001



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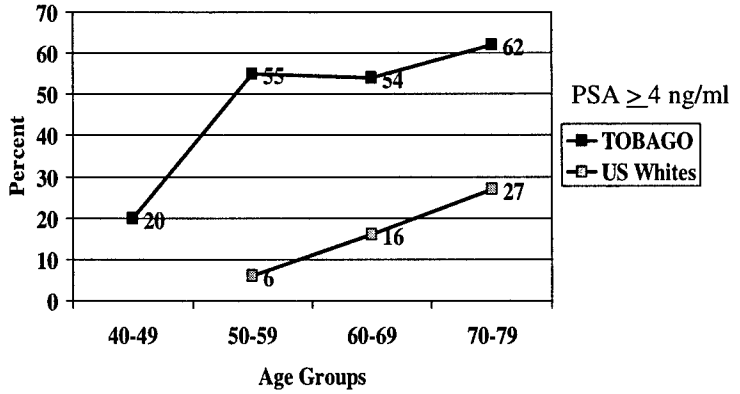
Cancer Detection Rate, PSA Screening, Tobago, February, 2001, US Whites, 1992 (Ritchie et al)



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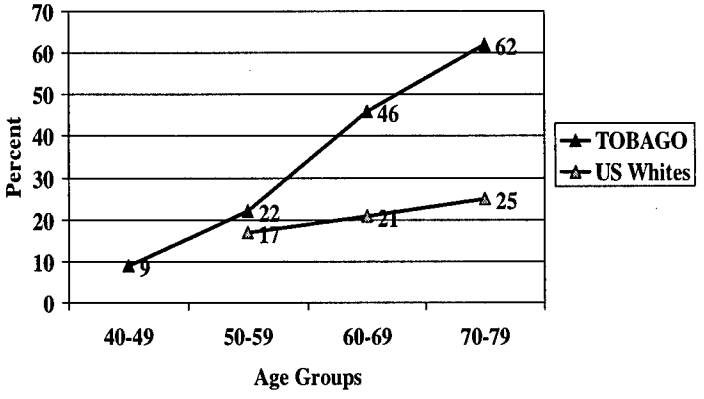
Cancer Detection Rate, DRE Screening, Tobago, February, 2001, US Whites, 1992 (Ritchie et al)



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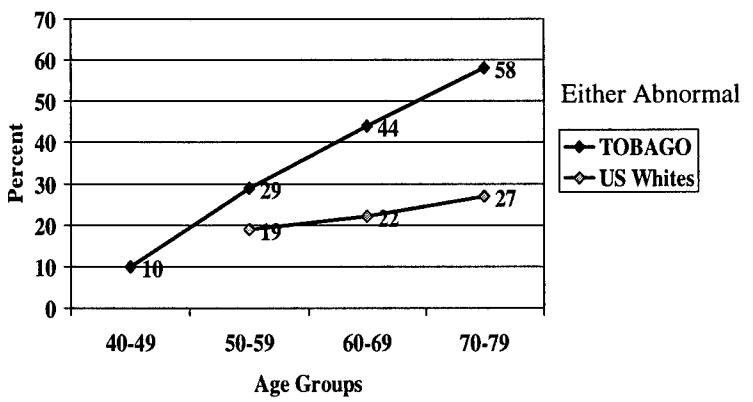
Cancer Detection Rate, PSA and/or DRE Abnormal, Tobago, February, 2001, US Whites, 1992 (Ritchie et al)



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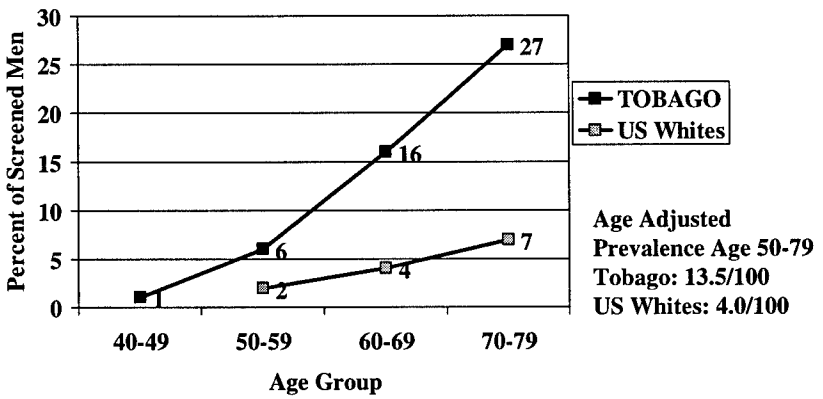
Screening Detected Prevalence of Prostate Cancer Among Tobago Men, 2001, and US Whites, 1992 (Ritchie et al)



Age Adjusted Prevalence Age 50-79
Tobago: 13.5/100
US Whites: 4.0/100

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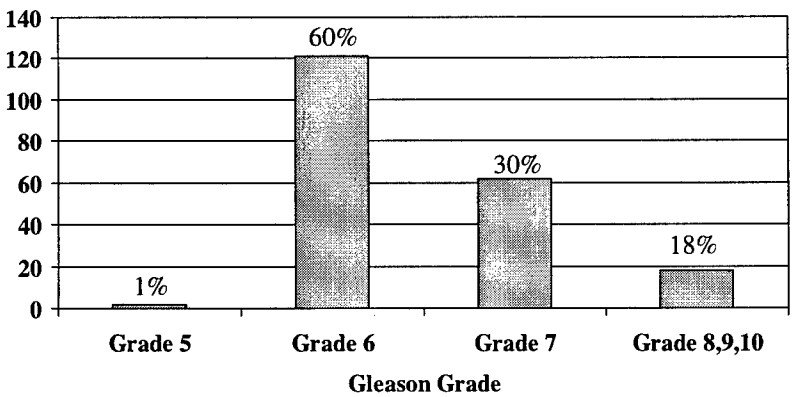
Distribution of Gleason Grade Among 203 Tobago Prostate Cancer Cases, February, 2001



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Tobago Prostate Survey Screening: Conclusion

- Prevalence of prostate cancer among Afro-Tobagonians is approximately three fold higher than prevalence in a large, similarly screened US Caucasian population.
- Why is prostate cancer risk elevated across populations of African descent in diverse settings?
  - Shared genetic factors?
  - Shared lifestyle factors?
  - Environmental factors?

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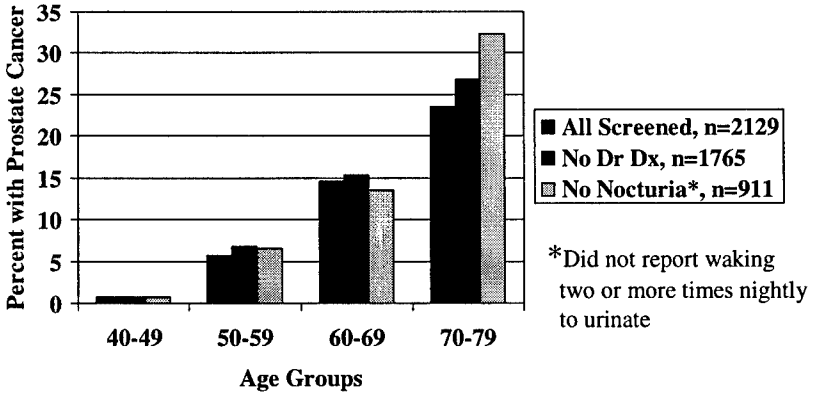
Screening Detected Prostate Cancer Rates in Asymptomatic Tobago Men, February, 2001



*Did not report waking two or more times nightly to urinate

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Human Herpesvirus 8 (HHV-8) is Associated with Risk for Prostate Cancer in Caucasian and Afro-Caribbean Men.

Jenkins FJ, Bunker CH, Patrick AL,
Dhir R, Trump DL, Becich MJ

University of Pittsburgh
Tobago Regional Health Authority

AUA Poster, Anaheim, June 3, 2001

Hypothesis

- HHV-8 DNA (Kaposi's sarcoma virus) has been found in human semen and prostate tissue
- Hypothesis
  - HHV-8 infection, as ascertained by serum antibodies, is associated with increased risk for prostate cancer.

AUA Poster, Anaheim, June 3, 2001

Populations

- US Caucasians
  - University of Pittsburgh tissue bank
  - Cases: 100 men with advanced prostate Ca
  - Controls: 99 men with other non-prostate/non HHV8 related cancers
- Trinidad & Tobago Afro-Caribbeans
  - Tobago population based prostate cancer screening study
  - Cases: 140 consecutive biopsy positive men
  - Controls: age matched, normal DRE and PSA $\leq$ 4 ng/ml

AUA Poster, Anaheim, June 3, 2001

Populations

- No known clinical Kaposi's sarcoma among participants
- No known HIV infection or clinical AIDS among participants
- Screening detected prevalence of prostate cancer in the Tobago population aged 50-79 (n=1645) is 13% (age-adjusted to US 1970 pop).
- Cancer detection in a similarly screened predominantly Caucasian US population (n=6501) was 3.5% (Richie et al, 1992) (age-adjusted to US 1970 pop).

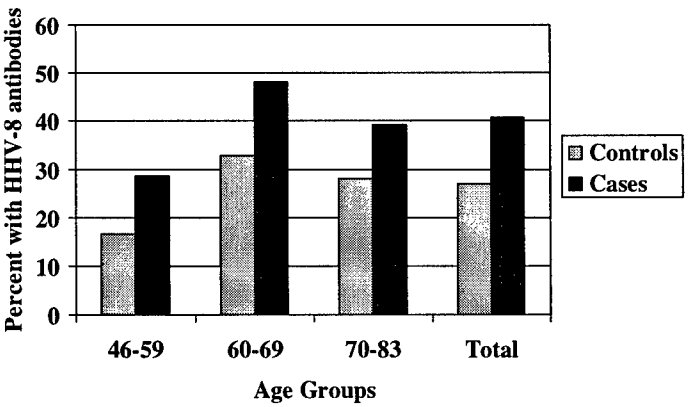
AUA Poster, Anaheim, June 3, 2001

HHV-8 Assay

- Antibodies assayed at the University of Pittsburgh by one of the authors (FJJ)
- HHV-8 antibodies measured blindly by indirect IFA assay (source??)
- Similar odds ratios confirmed by outside laboratory using a somewhat less sensitive HHV-8 antibody

AUA Poster, Anaheim, June 3, 2001

Frequency of HHV-8 Antibodies by Age Group in Tobago Cases and Controls



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Risk for Prostate Cancer Associated with HHV-8 Infection

- HHV-8 Infection
  - Caucasians
    - Cases 20/99 (20%)
    - Controls 12/100 (13%)
    - OR = 1.7 (95% C.I. 0.7 – 3.9)
  - Afro-Caribbeans
    - Cases 57/140 (41%)
    - Controls 38/141 (27%)
    - OR = 1.9 (95% C.I. 1.1-3.1)

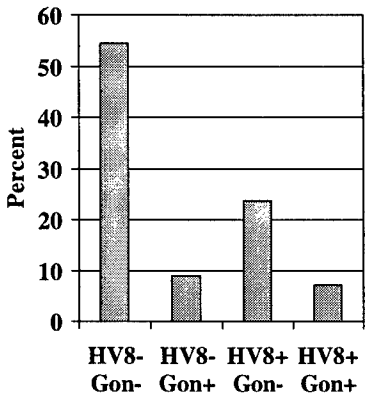
AUA Poster, Anaheim, June 3, 2001

HHV-8 and Gleason Group Among Tobago Men

- HHV-8 positive
  - Gleason group 5-7: 51/123 (41.5%)
  - Gleason group 8-10: 6/17 (35%)
- Frequency of HHV-8 antibodies not increased among men with higher Gleason grades

AUA Poster, Anaheim, June 3, 2001

Concordance for HHV-8 Antibodies and Reported HX of Gonorrhea



- Low concordance for HHV-8 infection and gonorrhea suggests that HHV-8 antibodies are not simply a marker for high risk sexual behavior

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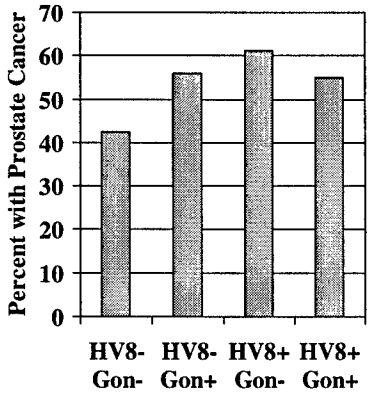
Prostate Cancer Risk with HHV-8 Infection and Reported HX of Gonorrhea



- Prostate cancer risk is associated with HHV-8 infection, but not associated with reported history of gonorrhea infection

AUA Poster, Anaheim, June 3, 2001

Summary

- Strength of association of HHV-8 infection with prostate cancer risk (nearly two fold) is similar in populations of Caucasian and African ancestry.
- The high rate of HHV-8 infection in the Tobago population may explain part of the observed excess risk for prostate cancer.

AUA Poster, Anaheim, June 3, 2001

Conclusion

- HHV-8 infection appears to be associated with both advanced clinical and preclinical prostate cancer.
- Investigation of the possible etiological role of HHV-8 infection in the initiation and/or early progression of prostate cancer is strongly recommended.

AUA Poster, Anaheim, June 3, 2001

Tobago Bone Health Study: Epidemiologic Study of High Bone Mineral Density on a Population Level

JA Cauley, JM Zmuda, A Patrick, VW Wheeler, D Hill, C Bunker
University of Pittsburgh and Tobago Regional Hospital

Population-based studies of individuals with high bone mineral density (BMD) could lead to the identification of factors, both genetic and environmental, which contribute to their high BMD. The Caribbean Tobago-Bone Health Study was initiated in 2000 as part of a prostate cancer screening study. This population of African descent shares considerable genetic heritage with African Americans (AA). Both populations are of West African descent. However, genetic admixture is low in the Tobago population compared to that in the AA population, estimated at 25%. To date, total hip BMD was measured by DXA (Hologic QDR 4500W, Bedford, MA) in 1195 men, age range 40 to 91 years. All of the men reported 100% African descent. We compared the mean total hip BMD across age groups in Tobago men with published data on white and AA men from the third National Health and Nutrition Examination Survey (NHANES III). (Figure) No data are reported for AA men age 80+, so we limited our comparisons to 1164 Tobago men age 40 to 79 years.

At every age, total hip BMD was 10-12% higher among Afro-Caribbean men compared to AA men. The absolute difference in hip BMD between Tobago men and AA men was approximately one full standard deviation (SD) difference. Compared to Caucasian men, the total hip among the Afro-Caribbean men was 17-20% higher with absolute differences >1 SD. Similar results were obtained for the femoral neck BMD. BMD declined across age groups in Tobago and US white and black men. The decline in total hip BMD across age groups 40-49 to 70-79 years was 7.3%, Afro-Caribbean; 9.2%, AA and 9.8%, white US men. The greater BMD among Tobago men could not be explained by differences in body weight, since the average body weight among the Tobago men (mean=80kg) was about 4-6 kg lower than US men. Among the Tobago men, total hip BMD increased with body weight. The mean total hip BMD among men with the lowest body weight (<68kg) was 1.04 g/cm^2 compared to 1.23 g/cm^2 among men with the greatest body weight (>91kg).

This population of Afro-Caribbean men may represent a population with the highest BMD known to date. Identification of the factors that contribute to their high BMD may extend to other populations and lead to preventive strategies.

2055 Characters + 300 for graph.

Submitted 4/2001. American Society of Bone and Mineral Research

DEPARTMENT OF THE ARMY
US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
504 SCOTT STREET
FORT DETRICK, MARYLAND 21702-5012

REPLY TO
ATTENTION OF:

MCMR-RMI-S (70-1y) 26 Aug 02

MEMORANDUM FOR Administrator, Defense Technical Information Center (DTIC-OCA), 8725 John J. Kingman Road, Fort Belvoir, VA 22060-6218

SUBJECT: Request Change in Distribution Statement

1. The U.S. Army Medical Research and Materiel Command has reexamined the need for the limitation assigned to technical reports written for this Command. Request the limited distribution statement for the enclosed accession numbers be changed to "Approved for public release; distribution unlimited." These reports should be released to the National Technical Information Service.

2. Point of contact for this request is Ms. Kristin Morrow at DSN 343-7327 or by e-mail at Kristin.Morrow@det.amedd.army.mil.

FOR THE COMMANDER:

Encl

PHYLIS M. RINEHART
Deputy Chief of Staff for
Information Management

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